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**PLASMAPHERESIS IN THE TREATMENT OF CRITICAL DEGREES OF ISCHAEMIA IN DIABETIC AND ANGIOPATHIES OF LOWER EXTREMITIES**

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Trophic and ulcerous-necrotic processes of the lower extremities may be observed in 25-66 % of patients with diabetes mellitus (3). The need for high amputation of the lower extremities exists in 25-37 % of the patients (15), a lethal end may be observed in 23,6-25 % (1,4).

The critical stages of ischaemia in patients with diabetes mellitus are characterised from extended haemorheological alterations, chronic intravascular hypercoagulation of the blood as well as the existence of an endogenous intoxication syndrome (5, 19). The endogenous intoxication syndrome is known to consist of different types of expression. In patients with diabetic angiopathies it is characterised from hyperglycaemia, ketonaemia, dysproteinemia as well as the existence of toxins of bacterial origin (13), circulating immune complexes (CIC), with capillarotoxic behaviour (7, 10), an increased percentage of killer cells responsible for the autoimmune destruction of  $\beta$ -cells of the pancreas (16). In this context there is no doubt about the need for an application of efficient detoxification and correction procedures for the altered haemostasis. According to our view plasmapheresis, which during recent years found a successful application in different pathological states of surgical patients (12, 17), can meet these demands to a considerable extent. According to the results of several authors (6, 18) the fractionation of the blood is haemorheologically oriented, adds to the extraction of bacterial toxins, paraproteins, CIC, killer cells etc. With the application of a gravitation-plasmapheresis in patients with a critical degree of anaemia in obliterating arterioscleroses and endarteritis of the lower extremities M.L. Kacilkin and the co-author (8) M.L. Loba, the co-author V.N. Melnikova as well as other authors (11) achieved in the majority of the patients a clearly positive result. This resulted in an increase of the oxygen tension in the tissues, an increase of the rheographic index, an improvement of the physical-chemical and biochemical properties of the blood, a ceasing of pain in the legs as well as in a decrease of the ischaemic and post-ischaemic intoxication. Furthermore we have not found any hints in the literature to the application of gravitation-plasmapheresis for the treatment of critical states of ischaemia of the lower extremities in patients with diabetes mellitus.

We examined 55 patients with diabetic angiopathies of the lower extremities; within the frame of the total therapy (angioprotectors, spasmolytics, anticoagulants, correction of the sugarplan) of the patients were treated with a single continuous flow extracorporeal plasma-pheresis treatment. The age of the patients was between 46 and 68 years. 12 were males and 14 were females. 14 suffered from diabetic microangiopathy, 12 from micro-macroangiopathy. An ischaemia of grade 3 was present in 11, one of grade 4 in 15 patients (classification according to F.W. Wagner (20)

with modification according to A.V. Pokrovskij (14)). Six patients suffered from ischaemic pain at rest, pale skin colour, edemas and hyperthermia of the skin surface of the terminal part of the lower extremities; seven presented with superficial ulcerations of the foot or the toes correspondingly (without visible inflammation); five suffered from deep ulcerations including the tendons and the bones; four patients demonstrated ulcerous-necrotic processes with the formation of phlegmonae and abscesses, in four patients gangrene of the toes or the distal part of the feet respectively were visible. The persistence of the diabetes mellitus was between an initial diagnosis up to 22 years. Insulin dependent diabetes (type 1) was seen in 10, a non Insulin dependent diabetes in 16 patients. A medium grade diabetes mellitus was found in 14, a severe diabetes in 12 persons. A combination of diabetic angiopathies of the lower extremities with retinopathy, neuropathy and myocardopathy was observed in the majority of the patients (22). No gravitation-plasmapheresis was used, in 29 (of 55) patients under standard treatment; these patients served as controls.

The indication for an extracorporeal plasmapheresis was considered when the following conditions were fulfilled: Traditional conservative standard therapy without success, the missing of a sharp limitation of the ulcerous-necrotic areas of the feet and the toes, a poor process of wound healing and the progress of tissue necroses after "small" surgical operations in the lower extremities. Plasmapheresis was performed with the system PF-0,5 from our national production. This enabled a continuous centrifugation of the blood in a continuous flow rotor with the simultaneous separation of single blood fractions (mass of erythrocytes and plasma) as well as a return of the erythrocytes together with Rheopolyglukin and Heparin (500 ED Heparin with 400 cc of plasma extending fluid). The continuous extracorporeal plasmapheresis was performed under continuous control of the subjective feeling of the patient as well as a monitoring-surveillance of pulse, temperature and respiration. Blood pressure, blood flow and anti-coagulation, erythrocyte- and plasma removal as well as the infusion of Rheopolyglukin and the rotor speed were controlled every 15 minutes. The total protein of the blood plasma, bilirubin, urea, creatinine, electrolytes, ALT and AST were measured prior to the plasmapheresis, after removal of half of the pre-planned plasma volume at the end of session, the following day and one and two weeks following plasmapheresis respectively. Blood glucose was measured prior to the treatment, after the removal of 500 ml plasma each, at the end of the plasmapheresis and subsequently 2-3 times per day, if necessary more frequently. The total cholesterol and the data of haemocoagulation were examined prior to the centrifugal separation, one day after the treatment and subsequently one or two weeks afterwards. Further more 15 patients were examined with dynamic rheovasography, 8 patients were examined by bicycle ergometry to follow the tolerance of physical challenge. During one plasmapheresis session between 1.200 and 2.200 ml of plasma were removed, which is 10-60 % of the OZP. The calculation of the circulating plasma volume was performed with Moore tables (2).

The continuous extracorporeal plasmapheresis in patients with diabetic and with critical ischaemia of angiopathies of the lower extremities demonstrated a moderate decrease of protein following the removal of 50 % of the planned plasma volume and a more extended decrease at the end of the centrifugal separation. On the following day the total protein of the blood returned to normal values, where it remained during the total time period (table 1). The same table demonstrates that the total cholesterol returned to normal within the days following plasmapheresis and remained in a range of physiological changes subsequently. A decrease of blood glucose was demonstrable at the end of the plasmapheresis treatment and during the following day. During this period of time the Insulin pre-treatment doses was not changed. Subsequently the blood glucose increased, however, remarkable changes could not be seen during this time period. The other biochemical blood values (total bilirubin, electrolytes, ALT and AST) demonstrated neither during the centrifugal treatment nor afterwards no significant changes from normal values.

Total blood coagulation tended to hypocoagulation during the next day as well as in the following week after plasmapheresis. In this context the kinetics of fibrinogen changes deserve special attention (table 2).

In the majority of the patients (12 of 15) rheovasography demonstrated during the first week after plasmapheresis an increase of the amplitude, an increase of the spikes, an increase of plethora and the elastic properties of the arteries of the terminal limb, the nitroglycerol test was rather weak in these patients. In the remaining patients (3) no essential changes of the rheovasograms occurred after plasmapheresis. The results of bicycle ergometry showed an increase of tolerance against physical challenge in all (8) patients. In 3 of the patients the total work volume increased one day after the centrifugal separation of the blood from  $1234 \pm 263$  kg/cm to  $2.100 \pm 216$  kg/cm, which means 1.6 fold. Five patients showed one week after plasmapheresis an increase of tolerance against physical challenge to  $2.216 \pm 224$  kg/cm. In 2 of 8 patients bicycle ergometry returned to the initial values by the end of the second week.

Table 1

**Kinetic of biochemical data of blood during the application of plasmapheresis**

BLOOD VALUE	INITIAL VALUE	AFTER COLLECTION OF 50% OF THE PLASMA VOLUME	AT THE END OF THE PLASMAPHERESIS TREATMENT
Total protein, g/l	$75 \pm 2$	$62,4 \pm 1,7$	$58,0 \pm 1,8$
Urea, mmol/l	$4,5 \pm 0,6$	$4,6 \pm 0,8$	$4,1 \pm 0,6$
Creatinine, mmol/l	$0,05 \pm 0,007$	$0,04 \pm 0,006$	$0,05 \pm 0,007$
Total bilirubin, mmol/l	$11,9 \pm 1,5$	$8,4 \pm 1,4$	$8,3 \pm 0,06$
Glucose, mmol/l	$14,4 \pm 2,6$	$13,5 \pm 2,6$	$9 \pm 1,7$
Total cholesterol, mmol/l	$6,6 \pm 0,6$	-	-
Kalium, mmol/l	$4,1 \pm 0,3$	$3,5 \pm 0,1$	$3,6 \pm 0,4$
Sodium, mmol/l	$136 \pm 2,0$	$134 \pm 1,9$	$140 \pm 0,2$
ALT, unit	$0,08 \pm 0,01$	$0,2 \pm 0,07$	$0,27 \pm 0,1$
AST, unit	$0,2 \pm 0,06$	$0,15 \pm 0,06$	$0,27 \pm 0,1$
BLOOD VALUE	NEXT DAY	1 WEEK LATER	2 WEEKS LATER
Total protein, g/l	$72 \pm 1,7$	$73,6 \pm 4,2$	$73 \pm 1,6$
Urea, mmol/l	$5,2 \pm 0,5$	$5,8 \pm 0,8$	$6,7 \pm 0,5$
Creatinine, mmol/l	$0,055 \pm 0,001$	$0,07 \pm 0,002$	$0,06 \pm 0,003$
Total bilirubin, mmol/l	$9,0 \pm 0,8$	$7 \pm 1,3$	$10,1 \pm 3,0$
Glucose, mmol/l	$10,5 \pm 1,8$	$12,5 \pm 2,2$	$11,7 \pm 2,6$
Total cholesterol, mmol/l	$4,7 \pm 0,5$	$5,7 \pm 0,1$	$5,1 \pm 0,3$
Kalium, mmol/l	$3,8 \pm 0,3$	$4,4 \pm 0,5$	$4,8 \pm 0,2$
Sodium, mmol/l	$141 \pm 0,2$	$134 \pm 0,3$	$136 \pm 0,1$
ALT, unit	$0,4 \pm 0,1$	$0,37 \pm 0,1$	$0,1 \pm 0,05$
AST, unit	$0,25 \pm 0,1$	$0,33 \pm 0,1$	$0,25 \pm 0,1$

The short term clinical result demonstrated that in 15 patients of 21 the pain in the legs was significantly reduced next day and in the following week after plasmapheresis, in 11 patients the oedema was reduced as well and the temperature in the distal areas of the committed limb increased. Eight patients demonstrated a separation as well as a sequestration of the surface necrosis of the toes and feet by the end of the second week. A demarcation of deep ulcerous-necrotic areas, a "restoration" of granulations as well as a formation at the edge-epithelisation of the wounds could be seen in 7 patients. Five patients switched from a wet gangrene of the toes to a dry necrosis. In 6 patients suffering from micromacroangiopathy no positive result could be seen; due to vital indications the shanks (3) or the thighs (3) were amputated. In 8 patients the limbs could be completely preserved; "small surgery" (necrotomy, excision of the pathologically altered tissue, exarticulation of the toes, resection of the feet) was performed in 12 patients, which led to the preservation of the limbs. There was no lethal outcome. The control group (29 patients) was characterised from 18 high amputations, "limited surgery" in 7 patients and restoration of the limbs in 4 patients. Five patients deceased in the control group following thigh amputation.

Table 2

**Kinetics of blood coagulation before and after plasmapheresis**

BLOOD VALUE	INITIAL VALUE	FIRST DAY	AFTER 1 WEEK	AFTER 2 WEEKS
Coagulation time, min	7,7±1,0	11,1±1,0	8,2±1,5	8,1±1,0
Recalcification time, min	2,2±1,0	2,8±0,3	2,4±0,2	2,5±0,2
Prothrombin, %	87±5	92±6	92±0,5	88±4
Fibrin stabilisation-factor (FSF); %	101±4	88,6±3	112±6	110±5
Fibrinogen, g/l	7,6±2	4,1±1	5±1	5,3±0,5
Fibrinolysis time, h	4,3±0,5	4,1±1	4,7±1	4,1±0,5
Thrombintime, s	27,3±3	29±2	28,3±1,5	27,2±1,5
Free heparin, s	6,8±1	7,2±1,5	8,2±2	5,6±0,5

During continuous extracorporeal plasmapheresis 4 patients suffered from hypoglycaemia (following fractionated infusion of the pre-calculated Insulin doses). A catheterisation of the peripheral veins for plasmapheresis was not always successful, in these cases (4 patients) the vena subclavia was punctured.

## Conclusions.

1. Extracorporeal plasmapheresis enables an immediate correction of the majority of the pathological biochemical data and of the coagulation of the blood in patients with diabetes mellitus.
2. Rheoplyglukin given during continuous flow plasmapheresis provides for the stability of haemodynamics and the stabilisation of the general state of the patient, thus it can be recommended as the major plasma exchange fluid for the fractionation of the blood in patients with diabetic angiopathy.
3. Within the frame of the total therapy of critical states of ischaemia in diabetic angiopathy of the lower limbs plasmapheresis enables to save the extremities and the reduction of the height of amputation respectively in the majority of the patients. Furthermore plasmapheresis must be performed in specialized hospitals which are able to provide for the appropriate monitoring and other devices and the provision of the corresponding amounts of the plasma exchange fluids as prepared from the transfusions specialists and surgeons.

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